REMARKS

The Examiner's attention to this Application is greatly appreciated.

I. STATUS OF THE CLAIMS

Claims 1 – 31 are cancelled. Claims 47 – 53, and 55 – 57 are withdrawn. Claims 32 – 46 and 54 are pending. All pending claims are rejected. Claims 32 – 34, 36, 38, 40 – 42, and 54 are amended herein. Claims 58 and 59 are new.

II. AMENDMENTS

Claims 32 – 34, 36, 38, 40 – 42, 44, and 54 are amended herein. New Claims 58 and 59 have been added. Care has been taken to avoid the introduction of new matter to the claims, and the amended claims are fully supported by the disclosure of the Application.

Claims 32, 38, 40 – 42 and 54 are all amended to clarify that the term "effective amounts" applies not the medicament in general, but particularly to the amount of 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid (hereinafter, "1-amino-olpadronate"). The Applicants submit that this rephrasing of the claims does not constitute new matter, and respectfully request the Examiner enter the amendments.

Claim 40 has been amended such that the phrase "who has recently undergone treatment with corticosteroids" is recited in the body of the claim and in the preamble, whereas before the phrase was recited only in the preamble. The Applicants submit that this rephrasing of the claims does not constitute new matter, and respectfully request the Examiner enter the amendments.

Claim 42 has been amended such that the phrase "said child" is replaced with the phrase "a child with a bone disease." As the preamble to the claim recites "a method for combating

bone disease in a child," this amendment adds no new matter to the claim. The Applicants respectfully request the Examiner enter the amendment.

Claims 33 and 34 have been amended to correct the misspelling of the word "administered." Claim 38 has been further amended to correct the term "this hydrates" to "its hydrates." Claim 44 has been amended to remove a misplaced dash. Claim 54 has been further amended to correct the phrase "treatment of bone disorder" to "treatment of a bone disorder." The Applicants submit that this rephrasing of the claims does not constitute new matter, and respectfully request the Examiner enter the amendments.

New Claims 58 and 59 depend on Claim 42, with the additional limitations of a dosage range of 0.01 – 1000 mg per oral application and 12.5 – 75 mg per oral application, respectively. These dosage ranges are supported by the Specification in paragraph 0046. The Applicants submit that the additional limitation does not constitute new matter, and respectfully request the Examiner enter the amendments.

III. REJECTION OF CLAIMS 38, 39, AND 54 AS NON-ENABLED

The Applicants note with agreement that the Examiner has decided that Claims 38, 39 and 54 meet the enablement requirement of 35 U.S.C. § 112 insofar as they claim the treatment of bone disorders. Office Action, page 3. The Office Action rejected Claims 38, 39 and 54 under 35 U.S.C. § 112 as non-enabled for the prevention of bone disorders and osteopathies. *Id.* The Applicants respectfully traverse the rejection.

A. THE OFFICE ACTION ADOPTS AN IMPROPER DEFINITION OF "PREVENT"

The non-enablement rejection is based on a definition of the term "prevent" that the Applicants submit is significantly different than the definition of the same term used in the art of medicine.

During examination, the claims must be interpreted as broadly as their terms reasonably allow. *In re American Academy of Science Tech Center*, 367 F.3d 1359, 1369, 70 USPQ2d 1827, 1834 (Fed. Cir. 2004). This means that the words of the claim must be given their plain meaning unless applicant has provided a clear definition in the specification. *In re Zletz*, 893 F.2d 319, 321, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989). "The ordinary and customary meaning of a claim term is the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application." *Phillips v. AWH Corp.*, 415 F.3d 1303, 75 USPQ2d 1321 (Fed. Cir. 2005) (*en banc*) (emphasis added). *Sunrace Roots Enter. Co. v. SRAM Corp.*, 336 F.3d 1298, 1302, 67 USPQ2d 1438, 1441 (Fed. Cir. 2003); *Brookhill-Wilk 1, LLC v. Intuitive Surgical, Inc.*, 334 F.3d 1294, 1298 67 USPQ2d 1132, 1136 (Fed. Cir. 2003)("In the absence of an express intent to impart a novel meaning to the claim terms, the words are presumed to take on the ordinary and customary meanings attributed to them by those of ordinary skill in the art") (emphasis added).

The Office Action includes a definition of the Examiner's understanding of the definition of the word "prevention": "In order to prevent a disease, as opposed to merely delaying or reducing its symptoms, a treatment must either render the subject completely resistant to said disease after a single treatment or limited number of treatments, or else, when continued indefinitely, continue to completely suppress the occurrence of said disease." Office Action, page 5.

The Office Action contains no allegation that this is the meaning of the term "prevention" held by one skilled in the art of medicine. The Office Action cites no authority of any kind to support this definition.

Extrinsic evidence determines the meaning of terms to persons having ordinary skill in the art. *Ferguson Beauregard/Logic Controls v. Mega Systems*, 350 F.3d 1327, 1338, 69 USPQ2d 1001, 1009 (Fed. Cir. 2003) (in which dictionary definitions were used to determine the ordinary and customary meaning of the words "normal" and "predetermine" to those skilled in the art). In construing claim terms, the general meanings gleaned from reference sources, such as dictionaries, must always be compared against the use of the terms in context, and the intrinsic record must always be consulted to identify which of the different possible dictionary meanings is most consistent with the use of the words by the inventor. "The ordinary and customary meaning of a claim term may be determined by reviewing a variety of sources. Some of these sources include the claims themselves, see *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1357 (Fed. Cir. 1999); dictionaries and treatises, *Texas Digital Systems, Inc. v. Telegenix, Inc.*, 308 F.3d 1193, 1202 (Fed. Cir. 2002); and the written description, the drawings, and the prosecution history, see, e.g., *DeMarini Sports, Inc. v. Worth, Inc.*, 239 F.3d 1314, 1324 (Fed. Cir. 2001)." *Ferguson Beauregard/Logic Controls v. Mega Systems*, 350 F.3d 1327, 1338, 69 USPQ2d 1001, 1009 (Fed. Cir. 2003).

The Office Action has offered no such extrinsic evidence, and therefore fails to meet the requirements of the case-law on the subject.

In compliance with opinions of the U.S. Court of Appeals for the Federal Circuit mentioned above, the Applicants hereby submit evidence that the meaning of the term

"prevention" in the medical arts refers to methods that lessen the probability or severity of disease, and not the clinically unattainable definition proposed in the Office Action.

As evidence the Applicants submit that the U.S. Patent and Trademark Office officially recognizes that the prevention of disease may involve "merely delaying or reducing its symptoms." It is written in MPEP 708.02 section X "The petition for special status should be accompanied by a statement explaining how the invention contributes to the diagnosis, treatment or prevention of HIV/AIDS or cancer." The Applicants submit that, according to the definition put forth in the Office Action, there are no technologies that prevent HIV/AIDS or cancer. The best efforts of medical technology can at best reduce the incidence of these diseases or reduce their severity. However, the USPTO has seen fit to accord special status to those applications that contribute to the prevention of AIDS and cancer. If the definition of the Office Action is adopted as valid, then the USPTO has created a category of application that does not exist.

As evidence the Applicants submit U.S. Patents 6,743,414, 6,846,496, 6,891,062, 7,056,882, and 7,158,835. All of these patents claim methods of preventing bone disease (osteoporosis). For reference, see the '414 claims 2, 5, and 6; the '496 claims 1, 11, and 12' the '062 claims 1, and 2; the '882 claims 1 and 3; and the '835, claim 1. However, none of these patents disclose how to make or use the inventions so as to "either render the subject completely resistant to said disease after a single treatment or limited number of treatments, or else, when continued indefinitely, continue to completely suppress the occurrence of said disease." Sadly, there is no known method that can prevent osteoporosis using the Examiner's proposed definition. Nonetheless, the various disclosures are presumably enabling by virtue of their status as issued patents.

As evidence the Applicants submit the definition of "preventive" from Taber's Cyclopedic Medical Dictionary, 14th Edition: "Hindering the occurrence of something, esp. disease." Taber's expounds on this concept in the definition of "preventive medicine":

> There are three levels of preventive effort. Primary preventive medicine is concerned with preventing the development of disease in a susceptible or potentially susceptible population... Secondary preventive medicine involves early diagnosis and prompt therapy to shorten duration of illness, reduce the severity of disease, reduce possibility of contagion, and limit sequellae. Tertiary preventive medicine is important in limiting the degree of disability and promoting rehabilitation in chronic and irreversible diseases.

Stedman's Medical Dictionary, 3rd Unabridged Lawyer's Edition, defines "preventive" as "1. Prophylactic; warding off disease. 2. A prophylactic, or anything that arrests the threatened onset of disease." The Applicants respectfully request the Examiner please consider these references texts as authoritative in their definitions of "preventive," and please adopt them as the definitions used by those skilled in the art.

As evidence the Applicants submit several entries from Stedman's Medical Dictionary (27th ed. 2000), a prominent medical reference text. The following definitions demonstrate that, in the context of the medical arts, the term "prevention" refers not to the ability to "either render the subject completely resistant to said disease after a single treatment or limited number of treatments, or else, when continued indefinitely, continue to completely suppress the occurrence of said disease," but to approaches that reduce the likelihood or severity of disease. The entries below include descriptions of effective preventative measures for such conditions as atherosclerosis, infectious disease, pregnancy, sexually transmitted disease, dental disease, hypertension, motion sickness, osteoporosis, emotional disorders, social deviance, stroke, and breast cancer. Sadly, these are not conditions that humanity is able to "prevent" within the Examiner's meaning. However, it is apparent that these diseases may be "prevented" within the

medical artisan's meaning. The only entry found in Stedman's that states there is no method of prevention is "Ebola virus." Please see the below entries in Stedman's (emphasis added):

ATHEROSCLEROSIS
...The prevention of atherosclerosis is a major objective of modern medicine. Preventive measures include regular vigorous exercise, a diet low in fat and cholesterol, maintenance of a healthful weight, avoidance of tobacco, and use of pharmacologic agents as indicated (e.g., rigorous control of hypertension and diabetes mellitus, reduction of elevated cholesterol, estrogen replacement therapy after menopause).

CHEMICAL PROPHYLAXIS
The administration of chemicals or drugs to members of a community to reduce the number of carriers of a disease and to prevent others contracting the disease.

COMMUNITY PSYCHIATRY
psychiatry focusing on the detection, prevention, early treatment, and rehabilitation of individuals with emotional disorders and social deviance as they develop in the community rather than as encountered one-on-one, in private practice, or at larger centralized psychiatric facilities; particular emphasis is placed on the social-interpersonal-environmental factors that contribute to mental illness.

CONDOM
Sheath or cover for the penis or vagina for use in the prevention of conception or infection during coitus.

CONTRACEPTION
Prevention of conception or impregnation.

DENTISTRY
The healing science and art concerned with the structure and function of the oral-facial complex, and with the prevention, diagnosis, and treatment of deformities, pathoses, and traumatic injuries thereof.

DRUG
1. Therapeutic agent; any substance, other than food, used in the prevention, diagnosis, alleviation, treatment, or cure of disease. For types or classifications of drugs, see the specific name.

HYPERTENSION
...Current practice standards call for still more diligent management, including prevention through avoidance of known risk factors, particularly in persons with a family history of hypertension, and control of cofactors known to increase the risk of cardiovascular damage in persons with hypertension (smoking, hypercholesterolemia, diabetes mellitus).

INOCULATE
To introduce the agent of a disease or other antigenic material into the subcutaneous tissue or a blood vessel, or through an abraded or absorbing surface for preventive, curative, or experimental purposes.

MECLIZINE HYDROCHLORIDE
An H_1 antihistaminic useful in the prevention and relief of motion sickness and symptoms caused by vestibular disorders.

OSTEOPOROSIS
...The goal of therapy in osteoporosis is prevention of fractures in susceptible patients... Hormone replacement with estrogen remains the most effective prevention and treatment for postmenopausal osteoporosis... The selective estrogen receptor modulator raloxifene has been approved for prevention of osteoporosis.

PROPHYLAXIS
Prevention of disease or of a process that can lead to disease.

PSYCHOPROPHYLAXIS
Psychotherapy directed toward the prevention of emotional disorders and the maintenance of mental health.

STROKE
...Effective measures for the prevention of stroke include aggressive management of hypertension, hyperlipidemia, and diabetes mellitus, cessation of smoking, and chemoprophylaxis in persons at high risk.

SULFACETAMIDE
An antibacterial agent of the sulfonamide group, primarily used topically; sulfacetamide sodium has the same uses as sulfacetamide and also is used locally for eye infections and for prevention of gonorrheal ophthalmia in newborn infants.

TAMOXIFEN CITRATE
A synthetic nonsteroidal estrogen antagonist used in the prevention and treatment of breast cancer.

EBOLA VIRUS
...Specific prevention and treatment are not available.

The Applicants submit that Stedman's illustrates the meaning of the term "prevention" to those skilled in the medical arts, and that prevention of chronic degenerative disease (including

the bone disease osteoporosis) is considered clinically attainable. Those of ordinary skill in the art consider osteoporosis to be preventable.

As evidence of the meaning of the term "prevention" in the medical arts the Applicants submit an illustrative article from a popular medical journal: N. Smith, J. Bresee, D. Shay, T. Uyeki, N. Cox, and R. Strikas, 2006 "Prevention and control of influenza" *Morbidity and Mortality World Report* 55: 1 – 42 (enclosed). This article details current recommendations for the prevention of influenza worldwide. Under the Examiner's definition, there is no means of "preventing" influenza. However, the article makes very clear that methods that achieve clinical results less than absolute perfection are considered methods of "prevention" in the art: "Influenza vaccination is the primary method for preventing influenza and its severe complications" *Id.*, page 2 (it is common knowledge that the influenza vaccine produces a clinical result short of the Examiner's definition); "Vaccination might prevent hospitalization and death among persons at high risk and might also reduce influenza-related respiratory illnesses and physician visits among all age groups, prevent otitis media among children, and decrease work absenteeism among adults" *Id.* p. 2 (note the use of the phrase "might prevent"); "Vaccine efficacy and effectiveness studies might have various endpoints, including the prevention of medically attended acute respiratory illness (MAARI), prevention of culture-positive influenza virus illness, prevention of influenza or pneumonia-associated hospitalizations or deaths, seroconversion to vaccine serotypes, or prevention of seroconversion to circulating influenza virus subtypes" *Id.* p. 7 (prevention of influenza is a clinically attainable goal); "influenza vaccine typically prevents influenza illness among approximately 70%--90% of healthy adults aged <65 years… However, among older persons not living in nursing homes or similar chronic-care facilities, influenza vaccine is 30%--70% effective in preventing hospitalization for pneumonia and influenza… In

this population, the vaccine can be 50%--60% effective in preventing influenza-related hospitalization or pneumonia and 80% effective in preventing influenza-related death, although the effectiveness in preventing influenza illness often ranges from 30% to 40%... The vaccine was 92% efficacious in preventing culture-confirmed influenza during the two-season study." p. 8 (less than 100% effectiveness is considered "prevention"); "The overall efficacy of LAIV and inactivated influenza vaccine in preventing laboratory-documented influenza from all three influenza strains combined was 85% and 71%, respectively, on the basis of experimental challenge by viruses to which study participants were susceptible before vaccination." p. 9 (same); " Chemoprophylactic use of antiviral agents is an option for preventing influenza among such persons." p. 20 (contrary to Examiner's assertion that "antiviral drugs are not normally administered to healthy subjects in order to prevent the development of infection"); "annual vaccination is the primary strategy for preventing complications of influenza virus infections" p. 29 (vaccination is considered prevention, although it is well known that the influenza vaccine is not 100% effective); "Chemoprophylactic drugs are not a substitute for vaccination, although they are critical adjuncts in preventing and controlling influenza" p. 32; and "In community studies of healthy adults, both oseltamivir and zanamivir are similarly effective in preventing febrile, laboratory-confirmed influenza illness (efficacy: zanamivir, 84%; oseltamivir, 82%)" p. 32 (less than 100% clinical perfection considered prevention).

The literature cited in the Application also makes reference to "prevention" as it is medically understood. As is evidenced by the definition in medical dictionaries, the use of the term in medical dictionaries and publications herein submitted, "prevention" refers to a tendency to significantly reduce the incidence or severity of a disease. Prevention does not refer to a

certainty that no patient to whom the drug is ever administered will ever suffer from even the slightest symptom of the disease.

The Applicants submit that evidence of the meaning of "prevention" in the medical arts contradicts the definition set forth in the Office Action, which is supported by no evidence. For the reasons stated above, the Applicants submit that the construction of the term "prevention" in the Office Action does not reflect the meaning of that term in the art.

B. THE OFFICE ACTION ADOPTS AN IMPROPER STANDARD FOR ENABLEMENT

The Office Action poses particular questions that can only be addressed through direct human experimentation. Office Action, page 5 – 6. The Applicants submit that this enablement standard does not comport with controlling law.

The U.S. Court of Appeals for the Federal Circuit has articulated the standard for enablement in a series of cases. The current Office Action's extremely high enablement requirement is contrary to the controlling law. "We do not hold that one must always prove that a disclosed process operates effectively to produce a claimed product." *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1217 (Fed. Cir. 2002); "The enablement requirement is met if the description enables any mode of making and using the claimed invention." *Engel Industries, Inc. v. Lockformer Co.*, 946 F.2d 1528, 1533 (Fed. Cir.1991) (*emphasis added*); "While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." *Genentech, Inc. v. Novo Nordisk A/S* 108 F.3d 1361, 1366 (Fed. Cir. 1997); "Whether making and using an invention would have required undue experimentation, and thus whether a disclosure is enabling under 35

U.S.C. § 112, ¶ 1, is a legal conclusion based upon underlying factual inquiries." *Johns Hopkins University v. CellPro, Inc.* 152 F.3d 1342, 1354 (Fed. Cir. 1998);

> The test [for undue experimentation] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention.

Johns Hopkins University v. CellPro, Inc. 152 F.3d 1342, 1360 (Fed. Cir. 1998);

> The disclosed molar concentration would provide sufficient information as to an initial dosage level so that one skilled in the art could determine, without inventive skill or undue experimentation, the necessary molar concentrations for the imidazole derivatives of the phantom count to achieve the desired pharmacological effect, i.e., the 50% inhibition of thromboxane synthetase in human or bovine platelet microsomes.

Cross v. Iizuka 753 F.2d 1040, 1052 (Fed. Cir. 1985); "Since one embodiment is admittedly disclosed in the specification, along with the general manner in which its current range was ascertained, we are convinced that other permutations of the invention could be practiced by those skilled in the art without undue experimentation." *See SRI Int'l v. Matsushita Elec. Corp. of America*, 775 F.2d 1107, 1121, 227 USPQ 577, 586 (Fed.Cir.1985) (the law does not require an applicant to describe in his specification every conceivable embodiment of the invention); *Hybritech Inc.*, 802 F.2d at 1384, 231 USPQ at 94 (the enablement requirement may be satisfied even though some experimentation is required)." *U.S. v. Telectronics, Inc.* 857 F.2d 778, 786 (Fed. Cir. 1988).

The Applicants submit that the Specification provides information needed by a person having ordinary skill in the art to use the claimed invention after a certain amount of routine experimentation. The Specification discloses recommended dosage amounts (paragraphs 0035, 0046, and 0047), and target extracellular concentrations (paragraphs 0044, 0068, 0082, 0086, and 0088).

The Applicants submit that Claims 38, 39 and 54 are enabled with respect to the prevention of bone disorders and osteopathies in light of the remarks and evidence presented above. The Applicants respectfully request the Examiner reconsider the rejection. The Applicants respectfully request the Examiner withdraw the rejection and allow the claims.

III. REJECTION OF CLAIMS 44 – 46 AS INDEFINITE

The Office Action rejected Claims 44 – 46 as indefinite, alleging that the recited extracellular concentrations fail to particularly point out and distinctly claim the invention under 35 U.S.C. § 112 paragraph 2. The Office Action explains "It is not clear how much of the [1-amino-olpadronate] needs to be administered to a patient to achieve such extracellular concentration. As such, one of ordinary skill in the art will not be apprised of the metes and bounds of the invention." Office Action, page 7. The Applicants respectfully traverse, and respectfully request the Examiner reconsider the rejection and withdraw the rejection.

The standard for indefiniteness is whether one of ordinary skill in the art could understand the meaning of the claim, not whether one having ordinary skill in the art would understand how to "achieve" a particularly claim limitation. The latter is the test of enablement. *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1366, 71 USPQ2d 1081, 1089 (Fed. Cir. 2004) ("The requirement to 'distinctly' claim means that the claim must have a meaning discernible to one of ordinary skill in the art when construed according to correct principles....Only when a claim remains insolubly ambiguous without a discernible meaning after all reasonable attempts at construction must a court declare it indefinite."). If the language of the claim is such that a person of ordinary skill in the art could not interpret the metes and

bounds of the claim so as to understand how to avoid infringement, a rejection of the claim under 35 U.S.C. 112, second paragraph, would be appropriate. See *Morton Int'l, Inc. v. Cardinal Chem. Co.*, 5 F.3d 1464, 1470, 28 USPQ2d 1190, 1195 (Fed. Cir. 1993).

The recitation of precise ranges of extracellular concentrations can be understood by those of ordinary skill in the art. Furthermore, a skilled artisan would be able to avoid infringement of the rejected claims with a basic understanding of the relationship between molar concentrations and dosage, assuming a margin of safety is employed.

The Office Action subtly misconstrues the standard for indefiniteness. A claim is not indefinite if a skilled artisan is unable to practice the claim (although in this case a skilled artisan could practice the claim with routine experimentation), a claim is indefinite if a skilled artisan is unable to avoid practicing the claim. The Applicants submit that the claimed range of 10^{-10} to 10^{-6} molar is not so vast that a skilled artisan would be unable to avoid infringing by simply taking into account the size of the dosage and the size of the patient.

IV. REJECTION OF CLAIMS 32, 35, 41 AND 54 AS ANTICIPATED BY VAN BEEK

The Office Action rejected Claims 32, 35, 41 and 54 as anticipated by International Publication Number WO 97/02827 by Van Beek (hereinafter "Van Beek"). The Applicants respectfully traverse, because Van Beek does not teach every element of the claims.

There is an essential difference between what is disclosed by Van Beek and what is claimed in the Application. The instant Application claims methods of using 1-amino-olpadronate to prevent, treat, and post-treat diseases and disorders of the bones. Van Beek teaches methods of using 1-amino-olpadronate for diagnosis, prophylaxis, and treatment of calcification disorders that do not benefit from the inhibition of bone resorption. Van Beek, page

5. Bone disorders generally do not fall under the category of disorders that do not benefit from the inhibition of bone resorption. Van Beek teaches that 1-amino olpadronate is useful to treat urolithiasis and ectopic calcification, which are diseases of the soft tissues. *Id.* Van Beek does not teach that 1-amino-olpadronate is effective to treat or prevent bone disorders, or maintain healthy bone structure.

It muddies the waters that Van Beek also teaches that 1-amino-olpadronate is useful as a carrier for other drugs that can effectively treat or prevent bone disease. However, the Examiner will please note that nowhere does Van Beek teach that 1-amino-olpadronate itself is useful for the diagnosis, treatment or prevention of bone disease. The specification of the Van Beek publication states clearly: "The present invention is related to the use of [1-amino-olpadronate]... or of its monosodium or other pharmaceutically acceptable salt, as a biological carrier for other bone active substances." Van Beek, page 3 (emphasis added).

The Applicants acknowledge that Van Beek contains language that could be misinterpreted as teaching the use of 1-amino-olpadronate as an active agent for the diagnosis, treatment, or prophylaxis of "all forms of osteoporosis, all forms of arthritis, and all forms of periodontal disease." Van Beek, pages 4 – 5. However, that this passage refers to the use of 1-amino-olpadronate as a biological carrier, not as the active ingredient (as is instantly claimed) is clarified later in the text:

> 1-amino-olpadronate can therefore be used in the treatment of conditions in which a potent antiresorptive action is unwanted while targeting to calcium crystals and/or retention of other properties is required. Examples include the diagnosis, prophylaxis and/or treatment of urolithiasis, ectopic calcifications, their use as specific carriers for other bone active molecules (including, but not restricted to, cytokines, growth factors, prostaglandins, hormones, etc.) or cytostatic drugs to the skeleton, either for diagnosis of therapeutic purposes, or when the specific properties of the R_2 group on bone metabolism should be retained (e.g. anabolic effect) such as in the treatment of all forms of osteoporosis, all forms of arthritis and periodontal diseases.

(emphasis added). The Examiner will please note that the salts of 1-amino-olpadronate are taught to be effective in their own right against soft-tissue disease such as urolithiasis, ectopic calcifications, but only useful as biological carriers for other active compounds against bone diseases, such as osteoporosis, arthritis and periodontal diseases.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). This document does not anticipate the instant claims, because Van Beek does not teach every element of Claims 32, 35, 41 and 54 as amended.

All of the rejected claims, as amended, are limited to the use of 1-amino-olpadronate for methods involving bone health. Claims 32 and 35 are drawn to "A method of maintaining healthy bone structure." Claim 41 is drawn to "A method for post-treatment of osteopathies." Claim 54 is drawn to "A method for prevention or treatment of bone disorder." In each case, the claims are limited to methods employing an amount of 1-amino-olpadronate that is effective to maintain, post-treat, or prevent problems of the bone. This is not the same as claiming 1-amino-olpadronate used as a carrier for other drugs that promote bone health.

The Amendments to the claims clarify that 1-amino-olpadronate itself must be present in an amount needed to promote bone health, and that the Applicants do not claim 1-amino-olpadronate as an inactive ingredient (such as a carrier) in a medicament useful for the maintenance of bone health and against bone disease. The Applicants claim 1-amino-olpadronate is amounts effective to maintain bone health and prevent or treat bone disease.

Claims 32 and 41 recite (and Claim 35 incorporates) the step of "administering to a patient a medicament comprising a bone health promoting effective amount of [1-amino-

olpadronate], any of its soluble salts or any of its hydrates." Claim 54 recites the step of "administering to a patient a medication comprising (a) a health promoting effective amount of [1-amino-olpadronate]."

Because Van Beek does not disclose that 1-amino-olpadronate itself in any amount can effectively promote the health of bones, this element of Claims 32, 41, 35 and 54 is not taught by Van Beek.

The Applicants respectfully request the Examiner reconsider the rejection under 35 U.S.C. § 102 of Claims 32, 35, 41 and 54, in light of the Applicants' amendment and explanation above. The Applicants submit that the Claims are patentably distinct from the alleged prior art reference. The Applicants respectfully request the Examiner withdraw the rejection and allow the claims.

V. REJECTION OF CLAIMS 33, 34, 36 – 40, AND 42 – 46 AS OBVIOUS

The Office Action rejected Claims 33, 34, 36 – 40, and 42 – 46 as obvious over Van Beek in light of the journal article by Brumsen. The Applicants respectfully traverse this rejection.

A. THE REJECTION IS MOOT IN LIGHT OF THE AMENDMENT

To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable

expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

In light of the instant Amendment, the rejection is moot, because it does not teach or suggest all claim limitations. As discussed in Section IV above, Van Beek does not disclose the claim limitation that 1-amino-olpadronate must be present in amounts effective to affect bone health. All of the rejected claims in amended form recite or incorporate this limitation. Claims 33, 34, 36 and 37 incorporate from Claim 32 the limitation of "administering to a patient a medicament comprising a bone health promoting effective amount of [1-amino-olpadronate]..." Claim 38 recites and Claim 39 incorporates the limitation of "administering to a healthy patient a medicament comprising an osteopathy preventing effective amount of [1-amino-olpadronate]..." Claim 40 recites the limitation of "administering to a patient in need thereof a medicament containing a bone-health promoting effective amount of [1-amino-olpadronate]..." Claim 42 recites and Claims 43 – 46 incorporate the limitation of "administering to said child a medicament comprising a bone-health promoting effective amount of [1-amino-olpadronate]..."

Because Van Beek does not teach that any amount of 1-amino-olpadronate is effective against diseases of the bone, Van Beek does not teach all limitations of the rejected claims.

B. 1-AMINO-OLPADRONATE IS NOT AN OBVIOUS VARIANT OF OLPADRONATE

The Examiner correctly points out that it has long been known that olpadronate is useful against diseases of the bone, and that olpadronate is chemically related to 1-amino-olpadronate. However, although these two compounds have similar structures, they have very different properties. 1-amino-olpadronate was previously believed to be of no use against diseases of the

bone because 1-amino-olpadronate has poor anti-resorptive properties. Prior to the instant invention, it was generally believed that 1-amino-olpadronate was only useful to serve as a mere carrier for more effective compounds when it came to addressing diseases of the bone.

"The presumption of obviousness based on a reference disclosing structurally similar compounds may be overcome where there is evidence showing there is no reasonable expectation of similar properties in structurally similar compounds." *In re May*, 574 F.2d 1082, 197 USPQ 601 (CCPA 1978). In light of the evidence presented below, it was not obvious to use 1-amino-olpadronate for the same purposes for which olpadronate had been used, because 1-amino-olpadronate was known to lack the antiresorptive properties of olpadronate. The two compounds in question were known to have quite different chemical properties. As such, it was not obvious to use one for the purpose of the other.

The poor ability of 1-amino-olpadronate to inhibit bone resorption, compared with the excellent ability of olpadronate to inhibit bone resorption, is illustrated in Van Beek Fig. 3, and is evidenced in the instant Application at paragraph 0083 ("As NH_2-OPD has been shown to be absolutely devoid of antiresorptive properties (Van Beek E. et al., 1996, *J. Bone Miner. Res.* 11, 1492-1497), particularly at doses at which, according to the present invention, some cellular effects on both osteocytes and osteoblasts are preserved it is here proposed to be a selective modulator of the osteoblast"). Bisphosphonates generally were believed to be of value against bones disease owing to their antiresorptive properties, but this property is absent from 1-amino-olpadronate.

The Office Action states in error that "Beek at al. discloses [1-amino-olpadronate] to have superior antiresorptive activity in direct comparison with olpadronate." Office Action, page 10. To the contrary, Van Beek discloses that 1-amino-olpadronate is significantly inferior to

olpadronate in its ability to inhibit bone resorption. Van Beek writes that 1-amino-olpadronate "was, however, additionally devoid of any antiresorptive activity..." Van Beek, page 5. This is illustrated in Figure 3 of Van Beek, which shows that 1-amino-olpadronate has no significant antiresorptive activity, whereas olpadronate has excellent antiresorptive activity. *Id.*, Fig. 3. Van Beek discloses unmistakably that olpadronate and 1-amino-olpadronate have completely different properties with regard to inhibition of bone resorption.

Van Beek and the instant Specification evince that olpadronate and 1-amino-olpadronate are functionally distinct, because the two compounds affect different cells. Olpadronate is an inhibitor of bone resorption, which is a process carried out by osteoclast. Specification, paragraph 0008; Van Beek, Fig. 3. In comparison, 1-amino-olpadronate functions as a modulator of osteoblast activity, but there is no evidence that 1-amino-olpadronate affects osteoblasts. Specification, paragraphs 0015, 0032, 0034, 0036, 0072 – 0093.

Because the two compounds are known to have different properties, it was not obvious to use one for the same purpose as the other.

The Applicants respectfully request the Examiner reconsider the rejection under 35 U.S.C. § 103 of Claims 33, 34, 36 – 40, and 42 – 46 as obvious over Van Beek and Brumsen, in light of the Applicants' amendment and explanation above. The Applicants submit that the Claims are patentably distinct from the alleged prior art references, and respectfully request the Examiner withdraw the rejection and allow the claims.

VI. CONCLUDING STATEMENTS

For the reasons stated above, the Applicants submit that the claims are patentably distinct from the prior art. The Applicants submit that all claims are in condition for allowance. As such, the Applicants respectfully request that all rejections be withdrawn, all claims allowed, and the Application passed to issue.

The Applicants believe this Response and Amendment to be filed timely, and no fees due. However, the Commissioner for Patents is hereby authorized to charge any amount due for retroactive extensions of time and any deficiency in any fees due with the filing of this paper or credit any overpayment in any fees paid on the filing or during prosecution of this application to Deposit Account No. 50-0951.

The Applicants are grateful for the Examiner's consideration of this matter. In light of the remarks above, the Applicants respectfully request the Amendments be entered, all rejections be withdrawn, and all claims be allowed. If the Examiner still has concerns as to the allowability of any claims, he is urged to telephonically contact the undersigned at the number below.

Respectfully submitted,

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